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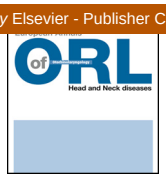

Original article

Extranodal non-Hodgkin lymphoma of the sinonasal cavities: A 22-case report

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ABSTRACT

Objective: To determine presenting features, management and prognosis in extranodal non-Hodgkin lymphoma of the sinonasal tract.

Material and methods: A retrospective study between 2004 and 2013 in the University Hospital Center of Nantes (France) recruited patients with lymphoma discovered by sinonasal involvement. Epidemiologic, diagnostic, clinical and prognostic criteria were analyzed, with survival studied on the Kaplan-Meier estimator and Log-rank test.

Results: Twenty-two patients were included: 14 male, 7 female, with a mean age of 65 years at diagnosis. All had non-Hodgkin lymphoma, with strong predominance of diffuse large B-cell lymphoma (77%). Seven patients had risk factors for lymphoma (infection by HIV, EBV or chronic lymphocytic leukemia). A majority (68%) had advanced tumor at diagnosis (stage IV on the Ann Arbor classification). Most were located in the craniofacial bones (68%), mainly involving the maxillary or ethmoidal sinuses. The most frequent presenting symptoms were unilateral nasal obstruction, mucopurulent rhinorrhea, recurrent epistaxis or diplopia. Treatment consisted in chemotherapy, in some cases associated to radiotherapy. Overall survival was 82% at 12 months and 73% at 36 months. Recurrence-free survival was 76% at 12 months and 64% at 36 months.

Conclusion: Lymphoma is an aggressive pathology; revelation by sinonasal involvement is rare. Recommended treatment is chemotherapy, possibly associated to radiotherapy. Prognosis depends on histologic type, Ann Arbor stage at diagnosis and the therapeutic options available for the individual patient.

1. Introduction

The head and neck region accounts for more than one-third of extranodal lymphomas. The nasal cavities and the sinuses, however, are rarely involved in Caucasian populations, representing only 0.2–2% of head and neck lymphomas [1].

Conversely, lymphoma accounts for 11% of sinonasal cancers [2], and thus come to be regularly encountered by ENT physicians, who should be ready to suspect this diagnosis in case of craniofacial bone tumor.

The main diagnostic problem is the lack of specific clinical signs, often leading to late consultation and thus diagnosis at an advanced stage.

Initial management should therefore be codified to avoid delay in treatment, as earlier diagnosis improves prognosis in this aggressive pathology. Lymphoma treatment is mainly medical, thus requiring close teamwork between surgeon and hematologist.

A retrospective study recruited all cases of sinonasal lymphoma diagnosed and/or treated between 2004 and 2013 in the University Hospital Center of Nantes (France). The objective was to determine clinical, pathologic, radiologic and prognostic characteristics, with a view to optimizing management.

2. Materials and methods

A retrospective study recruited patients diagnosed with lymphoma of the sinuses or nasal cavities in the University Hospital Center of Nantes between 2004 and 2013.

Patients were identified from the pathology department database. The inclusion criterion was diagnosis of lymphoma initially revealed by facial sinus or nasal cavity involvement.

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Table 1
Ann Arbor staging.

Stage	Definition
I	Disease in single lymph node or lymph node region
II	Disease in two or more lymph node regions on same side of diaphragm
III	Disease in lymph node regions on both sides of the diaphragm
IV	Disease is widespread, by hematogenic route, including multiple involvement at one or more extranodal sites
E	Extranodal invasion by contiguity
X	Large tumor (diameter > 10 cm mediastinal-thoracic ratio > 1/3)
B	With symptoms (weight-loss > 10%, sweats, fever)

Table 2
Signs on initial examination.

Initial clinical signs	Patients (*n*)	%
Endonasal mass	16	73
Nasal obstruction	8	36
Diplopia	6	27
Rhinorrhea	5	23
Epistaxis	5	23
Exophthalmus	5	23
Pain	4	18
Endo-oral swelling	4	18
Cranial nerve deficit	2	9
Epiphora	2	9
Adenopathy	1	4.5

Lymphomas that had invaded the nasal cavities or sinuses but with rhinopharyngeal, oropharyngeal or cutaneous origin were excluded, as were cases of sinus recurrence of nodal or extranodal lymphoma or sinonasal locations of other hemopathic malignancies.

All patients underwent ENT consultation for exploration of one or more chronic clinical sinonasal signs.

Age at diagnosis, presenting symptomatology, time from symptom onset to treatment initiation, risk factors, paraclinical assessment and treatment modalities were analyzed.

All biopsies were fresh samples studied under photon microscopy to analyze tumor architecture.

Immunohistochemistry determined phenotype (B or T), antibody expression (CD3, CD5, CD10, CD 20, Bcl2 and anti C-Myc) and proliferation index.

Paraclinical assessment enabled staging on the Ann Arbor classification (Table 1).

IPI (International Prognostic Index) was calculated, based on 5 factors: age (over 60 years), clinical stage (III/IV), performance index (equal to or greater than 2), LDH elevation, and involvement of 2 or more extranodal levels.

Files were discussed in multidisciplinary hematology team meeting to determine the appropriate treatment strategy.

Various factors were analyzed to determine their impact on survival: age, gender, Ann Arbor stage, IPI score, histologic type, sinus involvement, localized or diffuse form, and treatment implemented.

Survival was calculated following Kaplan-Meier and comparisons performed on Log-rank test.

3. Results

Between 2004 and 2013 in the Nantes University Hospital, 22 patients had histologic diagnosis of lymphoma of the nasal cavities and/or sinuses.

The male:female sex ratio was 2:1 (14 male, 8 female). Mean age at diagnosis was 59 years (range, 36–95 years).

Seven patients showed lymphoma risk factors: EBV or HIV infection, history of lymphopathy.

Presenting symptoms were poorly specific, with classic sinonasal functional signs: unilateral nasal obstruction, mucopurulent rhinorrhea, epistaxis and anosmia. However, these signs were systematically unilateral. A considerable number of patients (16 out of 22) showed non-rhinologic signs: diplopia (27%), exophthalmus (18%), endo-oral swelling (18%) or cranial nerve palsy (9%). Only 1 patient showed cervical adenopathy. Clinical examination found nasal cavity tumor syndrome in 16 patients (Table 2).

Depending on the patient, all sinuses showed involvement, with a clear predominance for the maxillary sinus (50%), followed by the ethmoidal sinus (23%), nasal cavities (18%) and sphenoidal sinus (9%). There was no frontal sinus involvement. Ten patients (45%) showed left-side and 12 (55%) right-side involvement.

Mean interval between symptom onset and diagnosis, reliably determined in 19 patients, was 4 months (range, 15 days to 27 months).

Craniofacial imaging was systematic: CT (14 patients) and/or IRM (8 patients), with remote extension assessment on cervico-thoraco-abdomino-pelvic CT; 10 patients had complementary PET-CT. 15 patients showed localized craniofacial involvement. Imaging indicated a homogeneous craniofacial tumoral mass, sometimes with spontaneous tumoral uptake (5 patients) or bone lysis (17 patients) (Fig. 1). Seven patients underwent osteomedullary biopsy; none showed medullary involvement. Lumbar fine-needle aspiration cytology, performed in 3 patients, was normal.

The lymphomas were all non-Hodgkin forms: 17 diffuse large B-cell (77%), 3 nasal NK/T and 2 plasmablastic.

Ann-Arbor staging (Table 1) found 2 stage IE tumors, 3 IIE, 1 IIIE and 16 IV.

A total of 15 patients had localized craniofacial tumor, although 11 of these were stage IV due to bone lysis (9 cases) or orbital infiltration (2 cases).

General signs (> 10% weight loss, sweats, fever) were rare, found in only 4 cases; LDH elevation concerned only 3 patients.

Treatment strategy was determined in multidisciplinary hematology team meeting. Three patients with localized craniofacial involvement received primary exclusive radiotherapy. Sixteen received primary exclusive chemotherapy (usually cyclophosphamide, doxorubicin, vincristine and prednisone or CHOP).

Eight patients showed incomplete response: 4 underwent salvage chemotherapy and bone marrow autograft, and 7 complementary craniofacial radiotherapy. One patient underwent surgical tumor resection, due to biopsy and multiple frozen section biopsies indicating malignancy, without further detail as to histologic type; lymphoma was diagnosed on definitive pathology examination.

Follow-up was clinical, biological and radiological, for a mean 30 months (range, 2–72 months). Two patients were lost to follow-up, and 1 was not followed up due to age (95 years).

Overall survival was 82% at 12 months and 73% at 36 months. Recurrence-free survival was 76% at 12 months and 64% at 36 months (Fig. 2: (A) overall survival, (B) recurrence-free survival).

Several factors tended to show positive association with survival: age (Fig. 3), male gender, IPI score < 2, histologic type diffuse large B-cell, and sinus involvement; the differences, however, were non-significant.

Survival in localized tumor (stage IE, or IV with exclusively craniofacial location) was 88% at 12 months and 80% at 36 months. There was no significant difference in overall survival between localized (IE) and advanced stages (IIE, IIIE and IV), ($P = 0.9$) (Fig. 3: overall survival according to (A) age and (B) stage).

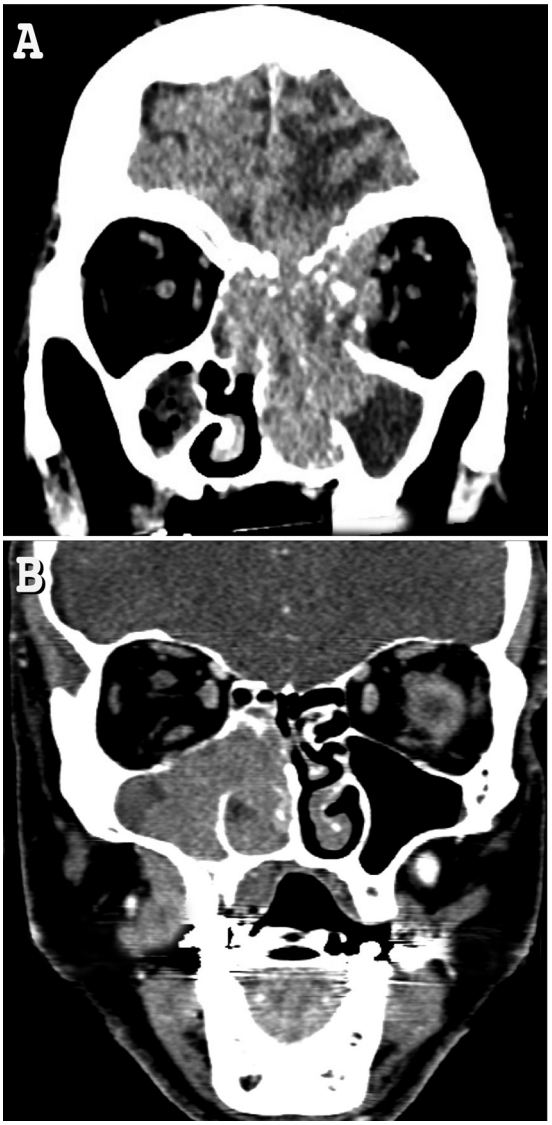

Fig. 1. Contrast-enhanced facial bone CT-scan, coronal slice showing (A) bone lysis of the skull base and medial orbital wall by ethmoidal-maxillary tumor: Ann Arbor stage IV lymphoma; (B) malignant right maxillary sinus tumor: diffuse large B-cell lymphoma.

4. Discussion

The head and neck region is a frequent site of tumoral invasion in lymphoma. Cervical lymph-node involvement is found in 39–72% of cases [3,4]. Extranodal involvement mainly concerns Waldeyer's ring [5]. Sinonasal involvement is rarer in Caucasian populations, at 0.2–5% of cases [1,6], unlike in Asian and South American populations, where it holds second place after digestive locations [6].

Histologic types are exclusively non-Hodgkin malignant lymphoma [6]. In Caucasian populations, diffuse large B-cell lymphoma is the prevalent type, while in Asia and South America nasal NK/T lymphoma predominates [1,6–11]. This pattern was found in the present series, with 77% diffuse large B-cell lymphoma and only 13% nasal NK/T lymphoma. Nasal NK/T lymphoma mainly involves the nasal cavities, whereas diffuse large B-cell lymphoma involves the sinuses [11,12].

The association of Epstein-Barr virus (EBV) infection with NK/T lymphoma is well-established [8,13], and was systematic in the present series.

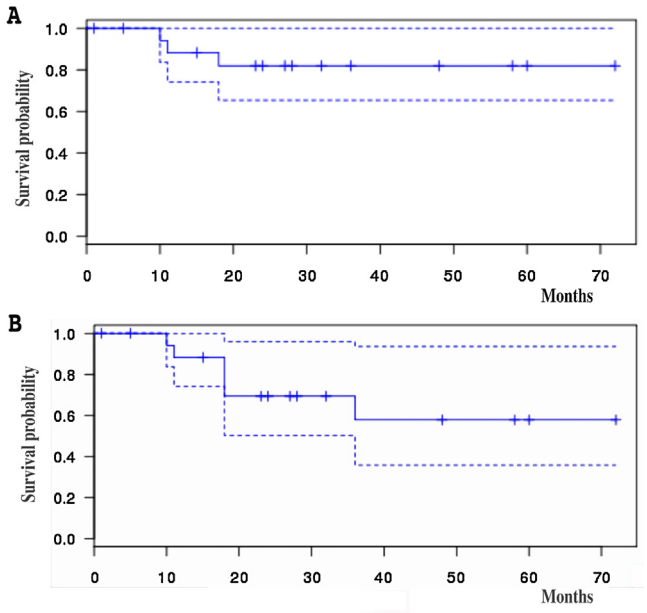

Fig. 2. Curves for (A) overall and (B) recurrence-free survival.

Two of the present series had human immune-deficiency virus (HIV) infection, and showed plasmablastic lymphoma. This is a rare hemopathy and a variant of diffuse large B-cell lymphoma, found almost exclusively in association with HIV infection [14]. Sinus involvement is exceptional, plasmablastic lymphoma being mainly revealed by oral cavity involvement [14].

Mean age at diagnosis ranges from 45 to 75 years, with clear male predominance [1,9–11,15,16], as in the present series with a 2:1 ratio and a mean age of 59 years.

Revelation is mainly by rhinologic signs (nasal obstruction, mucopurulent rhinorrhea, iterative epistaxis), sometimes accompanied by signs due to tumor volume (diplopia, exophthalmus, endo-oral swelling, neurologic deficit); unilateral presentation and treatment failure indicate complementary examination [1,12].

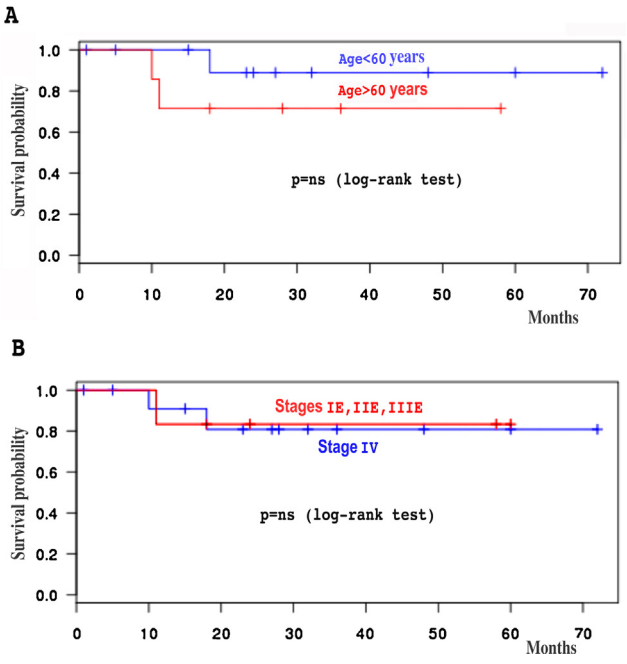

Fig. 3. Overall survival according to (A) age and (B) stage.

Moreover, endonasal examination, which can be performed in consultation, often finds a tumoral process (73%, in the present series). Cervical adenopathy was unusual (1 case), and has nothing specific to lymphoma [17]. The maxillary sinus is the most frequent location [1,11,16,18], as in the present series (50% of patients).

Morphologic assessment is the same as for other lymphomas, comprising contrast-enhanced CT-scan, completed by PET-CT [19].

Craniofacial imaging usually found homogeneous unilateral opacity, sometimes with spontaneous uptake (5 patients), and frequent bone lysis (17 patients). This aspect is not specific to lymphoma, but malignancy should be suspected in case of association of several radiologic signs: bone lysis, unilateral and/or heterogeneous opacity and heterogeneous contrast-medium uptake [2].

Osteomedullary biopsy is recommended in all forms of non-Hodgkin lymphoma, to explore for medullary involvement, with lumbar fine-needle aspiration cytology in head and neck locations or in case of neurologic signs [19].

Treatment is exclusively medical, based on chemotherapy and/or external radiotherapy [20]. Exclusive radiotherapy is a treatment of choice for localized forms with small tumor size (< 5 cm), as recommended by Quirashi et al. [1]; moreover, in elderly patients it has the advantage of lower toxicity. However, several studies have reported efficacy for combined treatment in localized forms with large tumor volume [1,12,16]. Chemotherapy is the treatment of choice in disseminated forms, the most usual protocol being CHOP. Some authors recommend systematic complementary craniofacial radiotherapy, even in disseminated forms [9,11,16]. In the present series, primary treatment was mainly chemotherapy (16 patients), due to patients' Ann Arbor stage. Radiotherapy was implemented secondarily for incomplete craniofacial response in 7 cases, achieving complete remission in 4. No survival gain for combined treatment versus exclusive chemotherapy could be demonstrated, for lack of power.

The classic major prognostic factors are Ann Arbor stage, IPI score, histologic type and symptoms at diagnosis [9,16]. A trend toward better survival could be seen for IPI score < 2 and diffuse large B-cell lymphoma (respectively 83% and 80% at 36 months), but did not prove significant. As in the present series, Kanumuri et al. [10] found no association between overall or recurrence-free survival and sinus involvement.

The present series included a high rate of advanced stages: 72% stage IV and only 9% localized IE stages. Other series reported a majority of localized stages, with 46–76% IE. Despite the present rate of IV stage lymphoma, 3-year overall and recurrence-free survival, at respectively 73% and 88%, were better than expected for such advanced disease; this may have been due to the stage-IV cases being mainly localized in the facial bones and graded stage IV due to bone lysis or orbital infiltration. Their staging was thus debatable, as extralymphatic infiltration was by contiguity and not hematogenic dissemination in 15 out of 16 cases. Logsdon et al. demonstrated the limitations of Ann Arbor staging in sinus lymphoma, comparing it with the AJCC 2007 TNM classification, which is the reference for craniofacial tumor: certain sinus lymphomas, although staged T4, may be IE according to the Ann Arbor classification; moreover, they reported 70% 5-year progression-free survival in IE-T4 tumor, versus only 29% in stage IV and 80% in other IE stages. In the present series, 3-year survival in localized craniofacial tumor was 80%, suggesting overstaging in 11 cases out of 15.

In conclusion, the present study, although biased by its retrospective design, confirmed that sinonasal lymphoma is a rare pathology, difficult to diagnose as revealing signs may mimic simple rhinosinusitis. Persistence or aggravation of symptoms, however, indicates at least one complete ENT examination, with flexible endoscopy. In case of unilateral nasal cavity lesion, fresh biopsy should be performed to screen for lymphoma.

In Caucasian populations, the most frequent histologic type is diffuse large-cell lymphoma, where prognosis is better than in the nasal NK/T forms predominating in Asia and South America.

Prognosis depends on histologic type, Ann Arbor grade, and general signs and IPI index at diagnosis. There is a risk of overstaging on the Ann Arbor classification, due to the frequency of bone or visceral involvement (brain, orbit) in sinus locations.

Treatment is based on an association of radio- and chemotherapy in most cases.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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